Syringocystadenocarcinoma Papilliferum In Situ-Like Changes in Extramammary Paget Disease: A Report of 11 Cases

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Abstract: The authors report 11 cases of extramammary Paget disease (EMPD), all of which also demonstrated a combination of histological changes highly reminiscent of syringocystadenocarcinoma papilliferum in situ. In addition to the classical features of EMPD, characterized by the intraepidermal spread of individually dispersed neoplastic cells with ample cytoplasm, many of which contained mucin, there were areas of acanthosis with the substitution of spinous layer keratinocytes by neoplastic cells, whereas the native basal cell layer was intact. In addition to acanthosis (and sometimes papillomatosis), the dermal papillae showed a prominent infiltrate of plasma cells, completing the resemblance to syringocystadenocarcinoma papilliferum in situ; this similarity was further enhanced in 2 cases, which showed conspicuous gland formation. One additional case showed multifocal dermal proliferations compatible with eccrine syringofibroadenoma (syringofibroadenomatous hyperplasia). The changes described herein seem to be relatively rare in EMPD, and they can represent a diagnostic pitfall, as evidenced by 2 cases that were originally misinterpreted as syringocystadenocarcinoma papilliferum in situ. Clinically, these microscopic changes sometimes corresponded to nodular lesions, which were specifically noted to have a papillated erosive surface.

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Syringocystadenocarcinoma Papilliferum In Situ–Like Changes in Extramammary Paget Disease: A Report of 11 Cases

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Key Words: extramammary Paget disease, syringocystadenocarcinoma papilliferum in situ, acantholysis, acanthosis, vulva, scrotum, eccrine syringofibroadenoma, anogenital mammary-like glands

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The authors declare no conflicts of interest.

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INTRODUCTION

In 1992, Rayne and Santa Cruz[1] described 6 cases of mammary Paget disease typified by mild epidermal hyperplasia, intraepithelial acantholysis, full thickness epidermal atypia, and marked cytological anaplasia, a histological variant which they termed anaplastic Paget disease. Similar mammary cases have since been reported, and more recently, Du et al[2] described an identical case of extramammary Paget disease (EMPD), which the authors likened to an acantholytic squamous cell carcinoma in situ. Both reports commented on the importance of recognizing this variant of Paget disease to avoid misinterpretation.

Other possible diagnostic pitfalls related to benign epidermal proliferative lesions in EMPD have been described, and these may be classified as fibroepithelioma-like changes, papillomatous hyperplasia, and squamous and psoriasiform hyperplasia.[3,4] In this report, we describe 11 cases of EMPD with unusual clinical and microscopic appearances. The latter included acanthosis of the epidermis, its colonization and substitution by neoplastic cells with an intact basal cell layer, and dermal papillae filled with plasma cells, a combination of features that imitate syrinocystadenocarcinoma papilliferum in situ.

MATERIALS AND METHODS

The 11 cases constituting the subject of this report were found among 174 cases lesions of EMPD in joint consultation and the institutional and personal files of the authors. Clinical information and follow-up data were obtained from the patients' physicians and/or review of case records. Each case was stained with hematoxylin and eosin and representative slides were stained with mucicarmine and immunohistologically for cytokeratin (CK) 7 and p63.

RESULTS

Clinical Data

The main clinical features of the cases are summarized in Table 1. There were 7 female and 4 male patients with ages at the time of the biopsy showing the syringocystadenocarcinoma papilliferum in situ-like changes ranging from 51 to 89

TABLE 1. Clinical Summary of 11 Patients With EMPD and Syringocystadenocarcinoma Papilliferum In Situ–Like Changes

Case	Sex/Age	Location	Clinical Presentation	Treatment	Follow-Up
Case 1	F/74	Perianal	Flat or slightly elevated erythematous or white-gray areas	Wide surgical excision	Recurrence at 4 yrs
Case 2	F/68	Vulva	An exophytic papillated nodule, clinically suspected fibroma; 8-yr history of EMPD treated with vulvectomy and RT; recent history of endometrial endometrioid carcinoma	Wide surgical excision	Recurrence at 2 yrs; DUC at 4 yrs
Case 3	F/79	Vulva	A 2.0-cm papillated superficially ulcerated nodule on the background of flat areas; 7-yr history of EMPD treated with vulvectomy, LN dissection and neovulva formation; breast carcinoma 1 yr previously	Wide surgical excision	Recurrence at 5 yrs in neovulva; NED for 2 yrs
Case 4	F/51	Vulva	Three-yr history of EMPD treated by vulvar resection	Vulvar resection	Recurrences at 3, 6–10 yrs.
Case 5	M/69	Groin/scrotum	Erythematous area	Wide surgical excision	NED at 8 mo
Case 6	M/75	Scrotum	3.5 × 2-cm plaque with cobblestone appearance; history of prostate and colon cancer	Surgical excision	Recent case
Case 7	F/80	Vulva	Flat discrete reddened lesion "discoid" in appearance	Wide surgical excision	Recurrence at 4 yrs; second recurrence at 7 yrs with concurrent diagnosis of breast carcinoma; no further treatment for EMPD (refused by patient); DUC at 5 yrs
Case 8	F/89	Labium major/groin	A 6 ×1.5-cm erythematous area on the right labium majus and two 2 × 2-cm areas in the right groin; 2-yr history of invasive (squamous?) carcinoma of the vulva treated by surgery and RT	Wide surgical excision	Lost to follow up
Case 9	F/83	Vulva	Red, thickened excoriated lesion; initial punch biopsy misinterpreted as VIN	Wide surgical excision	Probable local recurrence at 4 yrs clinically (not biopsied)
Case 10	M/78	Scrotum	Erythematous area; history of prostate carcinoma	Wide surgical excision	No evidence of EMPD; died at 9 yrs of prostate carcinoma
Case 11	M/88	Mons pubis	Erythematous area	Wide surgical excision	Recent case

LN, lymph node; RT, radiation therapy; NED, no evidence of disease; DUC, dead of unrelated cause; VIN, vulvar intraepithelial neoplasia.

years. Locations included vulva (6 cases), scrotum (3 cases), perianal area (1 case), and mons pubis (1 case). Eight of the patients presented with a newly diagnosed EMPD, whereas the other 3 had a previous history of EMPD treated by various modalities. Clinically, the lesions were characterized by flat or slightly elevated erythematous or white-gray areas, with some scaling, excoriations, and crust, but additionally on this background an exophytic nodule with a papillary surface was often present. One patient (case 6) had a history of prostate and colon carcinoma, and another (case 10) had a history of prostate carcinoma raising the possibility of secondary skin involvement from these sites. A further patient (case 2) had a recent history of endometrial endometrioid carcinoma whereas another (case 8) had invasive carcinoma of the vulva diagnosed and treated at an outside hospital (histology was not available for review).

Wide surgical excision was performed in all patients. Most individuals with available follow-up information had recurrence of the EMPD requiring further treatment. One patient (case 10) died of prostate carcinoma 9 years after the diagnosis of EMPD, and 2 patients (cases 2 and 7) died of unrelated causes.

Microscopic Features

All cases showed the classical morphology of EMPD characterized by an intraepidermal spread of individually distributed cells with ample cytoplasm, in many of which mucin could be demonstrated histochemically. Cytologically, the tumor cells were slightly to moderately pleomorphic; in one case, multinucleated giant cells were also seen. There was no invasion into the dermis but in all cases, adnexal structures (hair follicles and/or eccrine ducts) were involved by the neoplastic process.

In addition, in each case, there was an area of acanthosis and to lesser degree papillomatosis, with the substitution of the spinous layer keratinocytes by the Paget cells. However, the native basal cell layer was intact and encased the centrally located neoplastic cells. The dermal papillae showed

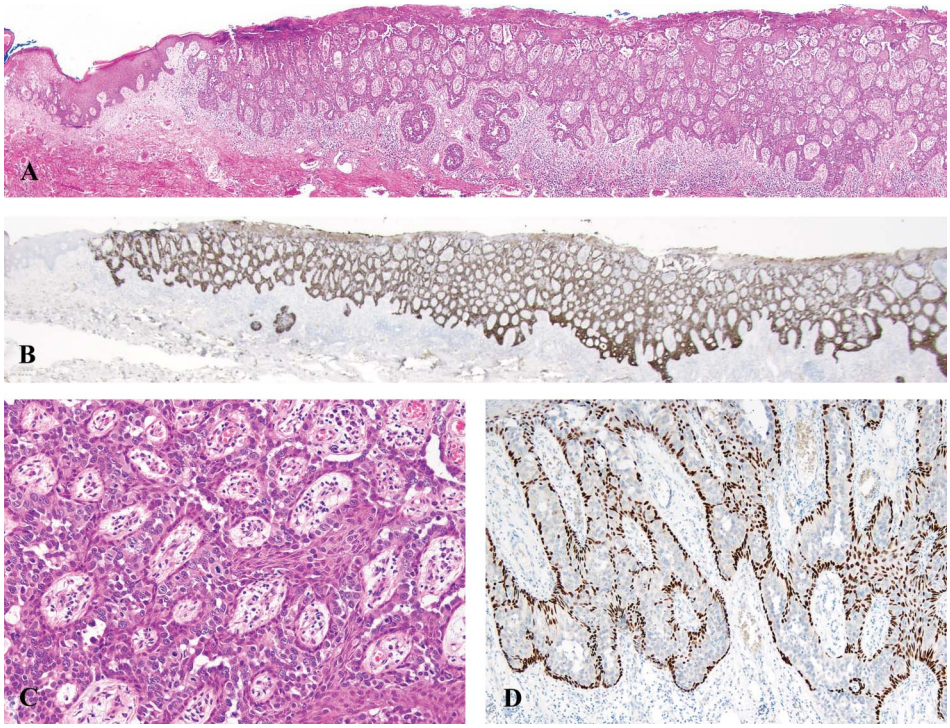

FIGURE 1. Extramammary Paget disease with areas resembling syringocystadenocarcinoma papilliferum in situ produced by epidermal hyperplasia associated with replacement of native spinous layer keratinocytes by Paget cells with only the basal layer being preserved. Note stromal papillae filled with a dense plasma cell–rich infiltrate (A, C). Staining for CK7 (B). Staining for p63 highlighting the preserved basal epithelium surrounding the neoplastic cells (D).

a prominent infiltrate of plasma cells, and thus the overall appearances were highly reminiscent of syringocystadenocarcinoma papilliferum in situ (Fig. 1). The above described changes were extensive in 8 specimens (cases 1–6, 10, and 11, Table 1) and focal in 3 specimens (cases 7–9). In addition, in 2 cases, the neoplastic cells focally grew in a dyscohesive fashion (acantholysis) with focal formation of gland-like structures and apocrine secretion (Fig. 2). One specimen (case 6), in addition to areas resembling syringocystadenocarcinoma papilliferum in situ, showed thin interconnected epithelial strands in a fibrovascular mucinous stroma, which resembled eccrine syringofibroadenoma (ESFA) (Fig. 3).

Immunohistochemical Findings

The neoplastic cells expressed CK7 and were negative for p63. The latter marker stained squamous cells in the epidermis and demonstrated that the basal cell layer was mainly preserved, whereas most native keratinocytes had been replaced by the Paget cells (Fig. 1).

DISCUSSION

The microscopic changes described in this report seem to be relatively uncommon being identified in only 11/174 (6.3%) EMPD cases examined by the authors. Although occasional similar cases have been previously documented, these have been subject to a different diagnostic interpretation. Du et al[2] described an almost identical case but the authors felt this most closely resembled an acantholytic squamous cell carcinoma in situ. In our opinion, the changes more closely mimicked syringocystadenocarcinoma papilliferum in situ due to the presence of acanthosis, the expansion of the

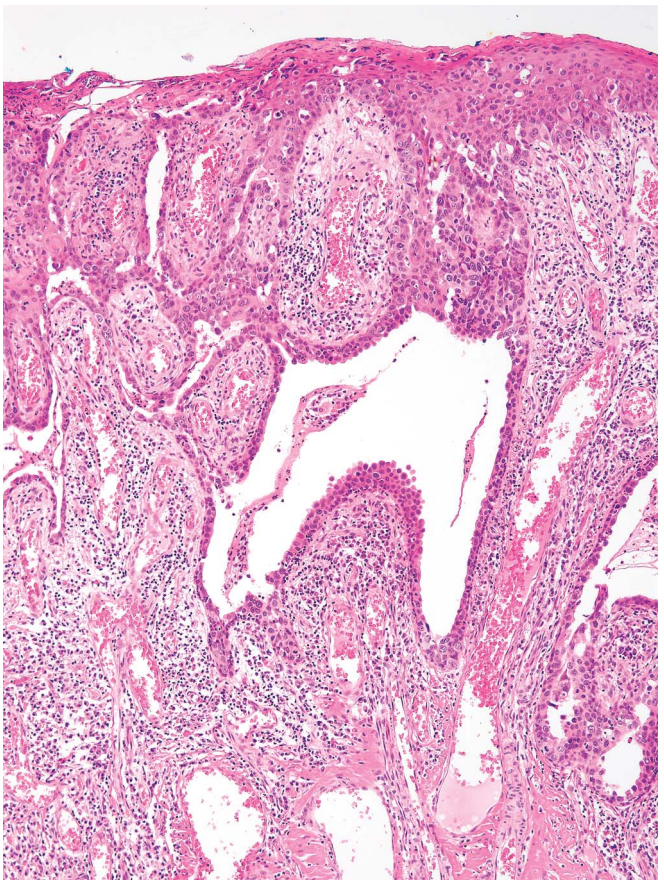

FIGURE 2. Large glandular structures with apocrine secretion in extramammary Paget disease.

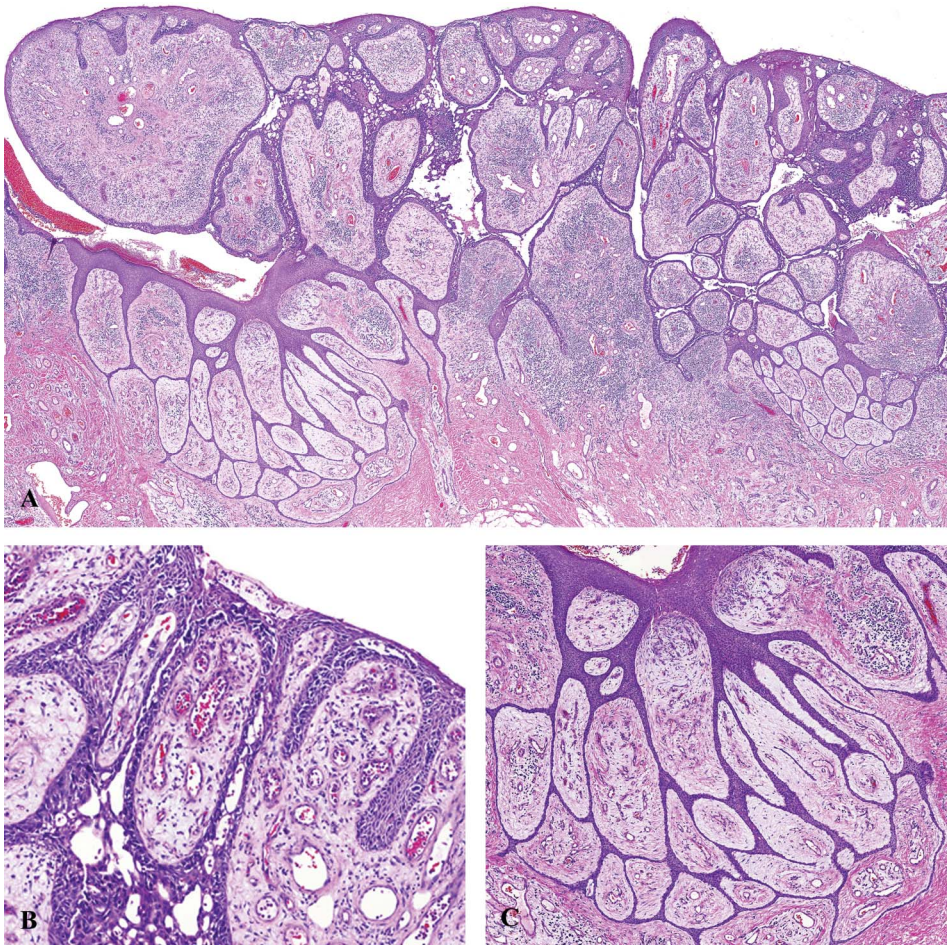

FIGURE 3. Extramammary Paget disease with areas resembling syringocystadenocarcinoma papilliferum in situ (A, B) accompanied by reactive proliferation of uninvolved eccrine ducts resembling eccrine syringofibroadenoma and typified by thin, interconnected epithelial strands in a fibrovascular mucinous stroma (C).

dermal papillae by plasma cells, and the preservation of the basal cell layer with encasement of the centrally located neoplastic cells thus imitating the basal/myoepithelial cell layers of that adnexal carcinoma.

Syringocystadenocarcinoma papilliferum is an extremely rare adnexal neoplasm,[5–14] and most lesions arise from a preexisting syringocystadenoma papilliferum associated with nevus sebaceus of Jadassohn and as such most occur in the head and neck. Although cases of syringocystadenocarcinoma papilliferum associated with pagetoid intraepithelial spread have been described in the anogenital region,[15,16] in our opinion, the illustrations provided with these reports suggest that these cases may instead represent EMPD with a similar phenomenon to that reported herein. Pagetoid spread of neoplastic cells in syringocystadenocarcinoma papilliferum in its classical location does occur but this is rare phenomenon.[7,12] The fact that 2 cases in this series referred in consultation were originally misinterpreted to be syringocystadenocarcinoma papilliferum indicates that this change in EMPD is underrecognized and represents a potential diagnostic pitfall histologically.

In 2 of our patients, the clinical findings were of a solitary nodular lesion with an ulcerated papillated surface on a background of flat or only slightly elevated lesions more typical of EMPD. Nodules in EMPD are rare, and histological correlation in such cases suggests that they are caused by an associated epidermal hyperplasia.[17] We posit that these epidermal changes represent a reactive process, most likely resulting from a combined response to direct epidermal destruction (or cytokine production) by the neoplastic cells, chronic rubbing by clothes, and/or skin erosion. The latter might lead to communication with the external environment and supervening infection, which in turn could sustain the secondary changes of epidermal hyperplasia and the influx of plasma cells into the dermal papillae. A similar phenomenon may be seen in other vulvar lesions[18] and also in cutaneous adnexal neoplasms, to wit tubular adenomas, which when acquiring a communication with the outside environment may develop appearances indistinguishable from syringocystadenoma papilliferum.[19] Lending further support to the reactive (hyperplastic) nature of the epidermal proliferative changes was the case in this series that demonstrated areas resembling ESFA. This lesion is considered by many to be a benign eccrine neoplasm but an alternative view is that it represents a reactive process involving the epidermis and eccrine ducts.[20,21] The latter conclusion is supported by the microscopic heterogeneity of cases reported as ESFA and their wide clinical associations, including burns,[22] erosive palmoplantar lichen planus,[23] bullous pemphigoid,[24,25] ulcers of various etiology,[26] lymphedema,[27] dermatofibroma,[28]

stoma,[29,30] podoconiosis,[31] amyloidosis,[32] and other conditions.[33] Some lesions have clearly been induced by irritation from urine, feces, mechanical friction, or trauma.

In conclusion, morphological changes reminiscent of syringocystadenocarcinoma papilliferum in situ are occasionally seen in EMPD. The histological changes represent a potential diagnostic pitfall, and it is essential that these are recognized to avoid misdiagnosis and mistreatment.

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